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published in

From Computational Biophysics to Systems Biology (CBSB08),
Proceedings of the NIC Workshop 2008,
Ulrich H. E. Hansmann, Jan H. Meinke, Sandipan Mohanty,
Walter Nadler, Olav Zimmermann (Editors),
John von Neumann Institute for Computing, Jülich,
NIC Series, Vol. **40**, ISBN 978-3-9810843-6-8, pp. 153-156, 2008.

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http://www.fz-juelich.de/nic-series/volume40

Effect of Temperature on the Structural and Hydrational Properties of Human Islet Amyloid Polypeptide in Water

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Structural and hydrational properties of the full-length human islet amyloid polypeptide 1-37 (hIAPP) were studied in a temperature range from 250 to 450 K by molecular dynamics computer simulations. At all temperatures studied, hIAPP does not adopt a well-defined conformation. The distribution of residues having the dihedral angles ϕ and ψ within the allowed regions of the Ramachandran plot which define β-sheets and poly(L-proline) II structures along the peptide chain is close to random, whereas a clear trend towards cooperative "condensation" is seen for residues having Ramachandran angles which characterize α-helices. This cooperativity and the number of intrapeptide H-Bonds is suppressed by heating or by introducing the natural intramolecular disulfide bond between residues 2 and 7. Intrinsic volumetric properties of hIAPP were estimated by taking into account the difference in the volumetric properties of hydration and bulk water. The temperature dependence of the density of hydration water indicates that the effective hydrophobicity of the hIAPP surface is close to that of carbon-like surfaces. The thermal expansion coefficient of hIAPP is found to be negative and decreases continuously upon heating from $\sim -3 \cdot 10^{-4}$ to $\sim -2 \cdot 10^{-3}$ K^{-1}. The spanning H-bonded network of hydration water at the hIAPP surface breaks via a percolation transition at about 320 K, which may be related to the drastic speed up of hIAPP aggregation seen experimentally in this temperature region.

1 Introduction

The aggregation of the human islet amyloid polypeptide (hIAPP) is involved in Diabetes Mellitus Type II. Hence, knowledge of the conformational behavior of this peptide is important for understanding the aggregation mechanism of hIAPP and for finding the means to prevent formation of its ordered fibrillar aggregates, which may be the main cause of decease. Experimental studies of the structural properties of hIAPP have not been successful due to its strong propensity to aggregate.

2 Systems and Methods

In this work, we performed MD computer simulation studies of the structural and hydrational properties of a single hIAPP peptide in liquid water in the temperature range from 250 to 450 K. All atomic molecular dynamics simulations were carried out with GROMACS v.3.3.1 using the OPLS-AA/L force field for the peptide and SPCE water molecules. Initially, the peptide was prepared in various starting conformations, including an α-helical conformation, four random conformations obtained from 1 ns runs at 1000 K *in vacuo*, of which one of the initial conformations being a fully extended isolated β-strand. After 15 to 30 ns simulation runs in water, the conformational behavior of hIAPP no longer depended on the initial configuration used. After 50 ns of equilibration at each temperature studied,

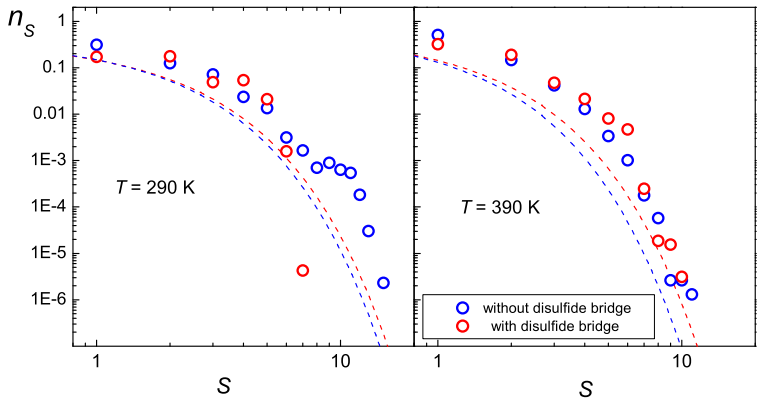

Figure 1. Probability n_S to find S successive residues with helical conformation. The dashed lines show n_S for a random distribution of residues in an infinite chain with the same content p of residues with analogous structure: $n_S = (1 - p)^2 p^S$.

200 ns trajectories were used for the analysis of the system properties. Two moieties of hIAPP were studied: hIAPP with and without the natural disulfide bridge between C2 and C7 residues.

3 Structural Properties

Analysis of the secondary structure shows that at all the temperatures studied, hIAPP does not adopt a well-defined conformation. The helical content of hIAPP, estimated as a fraction of residues having the dihedral angles within the allowed region of the Ramachandran plot, do not depend noticeably on the presence of a disulfide bridge and decrease upon heating. However, the ability of the helical residues to form a continuous sequence along the peptide chain is strongly suppressed by the disulfide bridge. This can be seen from the comparison of the probability distributions n_S to find S successive residues with helical conformation shown in Fig. 1. Large clusters of residues with helical dihedral angles disappear by introducing the disulfide bridge and by heating.

4 Volumetric Properties

The intrinsic volumetric properties of a biomolecule in water can be studied, when the density of hydration water is known.[1] The temperature dependence of the density ρ_h of the hydration water in a shell 0.3 nm thick at the hIAPP surface and of the density ρ_b of a bulk liquid water are shown in Fig. 2: ρ_h is below ρ_b and its temperature dependence is essentially linear. The temperature dependence of the density of hydration water indicates that the effective hydrophobicity of the hIAPP surface is close to that of carbon-like surfaces. Knowing the temperature dependences of ρ_h and ρ_b, we can estimate the intrinsic volume V_{int} of hIAPP from the equation: $V_{int} = V_{app} - \Delta V$. Here, V_{app} is the apparent volume of hIAPP measured as the difference between the volumes of the simulation boxes

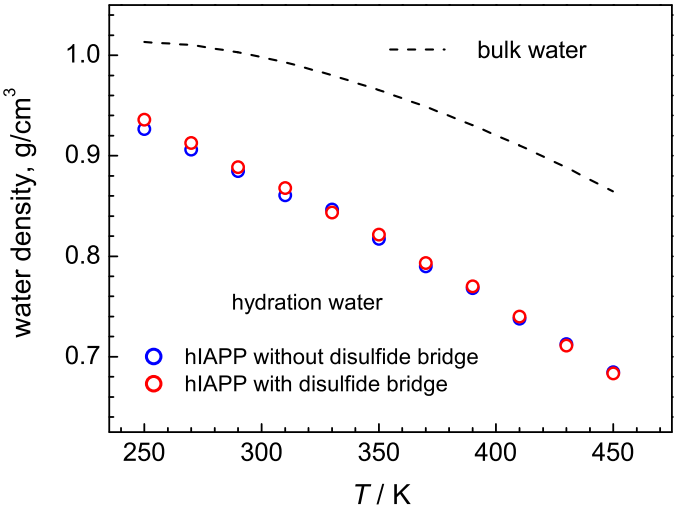

Figure 2. Temperature dependence of the density of bulk water and hydration water near hIAPP.

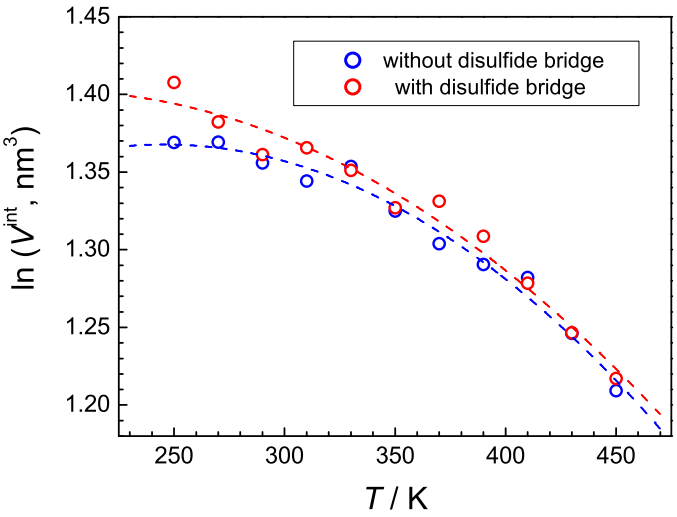

Figure 3. The temperature dependence of the logarithm of V_{int} of hIAPP. The lines are the fits to a quadratic polynomial.

with and without hIAPP, respectively, both having the same number of water molecules. The term ΔV accounts for the change of the system volume due to the different densities of hydration and bulk water, $\Delta V = V_h(1 - \rho_h/\rho_b)$, where V_h is the volume of hydration water. In a first approximation, V_h is the product of the solvent accessible area and the thickness of the hydration shell. The temperature dependence of the logarithm of V_{int} of

hIAPP is shown in Fig. 3. The slope of this dependence is equal to the intrinsic thermal expansion coefficient α_{int}. Similarly to the case of amyloid β peptide (1-42)[1], α_{int} of hIAPP is negative and becomes even more negative upon heating. Such behavior can be attributed to a decreasing helical content and a decreasing number of intrapeptide H-bonds. Note, that the disintegration of large clusters of helical residues by the disulfide bridge at low temperature (see Fig. 1) makes α_{int} more negative (see Fig. 3).

5 Thermal Disruption of the Hydration Water Network at the hIAPP Surface

The spanning H-bonded network of hydration water, which covers hIAPP homogeneously at low temperatures, breaks via a quasi-2D percolation transition, whose midpoint is located at about 320 K. Interestingly, approximately at this temperature, the experimentally measured lag time of hIAPP aggregation drops drastically[2]. Hence, we might conclude that the breakdown of the spanning H-Bonding network of hydration water might foster hIAPP aggregation.

Acknowledgments

Financial support from the International Max-Planck Research School in Chemical Biology and from the Federal State of NRW and the EU (Europäischer Fonds für regionale Entwicklung) is gratefully acknowledged.

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